USE OF ANTI-ASTHMATIC MEDICATIONS IN ELDERLY TAIWANESE PATIENTS

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The aim of this study was to assess the use of anti-asthmatic medications in Taiwanese geriatric asthmatic patients. We used computerized prescription databases from the National Health Insurance Program, Taiwan, and classified drugs according to the Anatomical Therapeutic Chemical Classification System to analyze the patterns and extent of medication use in people aged over 65 years, and the influence of physician specialty on the prescription of anti-asthmatics. A total of 708,624 prescriptions for 226,018 patients were analyzed. Oral medications were most often prescribed. Only 3.94% and 7.79% of patients were treated with inhaled corticosteroids and inhaled short-acting β-agonists, respectively. Pulmonologists prescribed significantly more inhaled anti-asthmatics, except for cromolyn, than other types of physicians. More males than females were prescribed each category of anti-asthmatic medications, except for ketotifen. In conclusion, physicians in Taiwan do not prescribe as many inhaled anti-inflammatory agents for the treatment of asthma in the elderly as suggested in international treatment guidelines.

Key Words: asthma, geriatric, medication
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Asthma is a significant cause of morbidity and healthcare utilization in the elderly. Asthma-related hospitalizations of older patients have serious financial consequences for the healthcare system [1]. Despite improved medical technologies to manage asthma and advances in the understanding of its pathophysiology over the past decade, asthma-related mortality in the elderly population continues to rise [2]. The cause for this ever-increasing mortality is not well understood. It is probably associated with the under-recognition and under-treatment of asthma by patients and physicians [3–5]. Contributory factors to this underestimation may include the overlapping of asthma symptoms with those of chronic obstructive pulmonary disease (COPD), comorbidities such as angina, and congestive heart failure that may mimic asthma, and reduced subjective awareness of moderate acute bronchoconstriction in old age [6–8].

Although the pathogenesis and therapeutic response of asthma often differ between elderly and younger patients, the basic principles of asthma therapy for geriatric asthmatic patients are similar to those for younger individuals. Treatment should adhere to the stepwise recommendations, starting with inhaled short-acting β-agonists (ISBAs) for mild intermittent asthma, and advancing to include inhaled corticosteroids (ICSs) or oral corticosteroids (OCSs) for mild to severe persistent asthma [9]. ICSs remain the most effective agents to control inflammation in the elderly. Anti-inflammatory agents are generally

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underused and bronchodilators are overused [5,10–15].

In Taiwan, the proportion and number of individuals over 65 years old are steadily increasing. It was estimated that, as of May 2002, people older than 65 years in Taiwan accounted for 8.88% of the population [16]. In terms of healthcare and its financing, this is an issue of great concern. The burden to the patients themselves, with regard to medical cost and reduced quality of life, is high. The aging population means that these problems can be expected to increase in coming years. To date, little is known about medication use among the asthmatic elderly in Taiwan.

The emergence of computerized prescription databases allows population-based analysis of individual drug use. Computerized individual healthcare data, including diagnosis and prescription data, have been available in Taiwan since the implementation of the National Health Insurance (NHI) Program in 1995. The data collected by the Bureau of National Health Insurance (BNHI) in Taiwan have provided unprecedented opportunities to conduct population-based studies of healthcare utilization. The purpose of this study was to determine whether Taiwanese geriatric asthmatic patients receive optimal pharmacotherapy.

Materials and Methods

Data source

The NHI Program, which is a mandatory universal health insurance program, was implemented in Taiwan on March 1, 1995, and covers more than 95% of the population (96.16% at the end of 2000) [17]. The BNHI has become the sole buyer of health services. In 1997, contracted medical care providers included about 96.5% of hospitals and 89.5% of clinics [18].

Each month, contracted medical care providers must file a computerized claim form to the BNHI. The information on the computerized claim form includes date, personal identification number (ID), age, sex, medical care provider's ID, prescribed drug's therapeutic code, diagnosis, and medical expense claims.

Materials

The data files used in this study were retrieved from the database of the BNHI, which manages the database on behalf of the Department of Health. Under the regulation of the Personal Electric Data Protection Law, strict confidentiality guidelines were followed. Both the personal and medical care provider's IDs in the database were scrambled. The study included all prescriptions for asthma patients (ICD-9 493) who were older than 65 years between February 1 and June 30, 1998.

Prescription drugs were classified according to the Anatomical Therapeutic Chemical Classification System [19], allowing international comparison. They included ISBAs and oral short-acting β-agonists (OSBAs), inhaled ipratropium, methylxanthines, ICSs and OCSs, inhaled cromolyn, and ketotifen. Leukotriene modifiers and nedocromil were not available in Taiwan during the study period.

Statistical analysis

The Chi-squared test was used to determine the odds ratios for the different asthma treatments for females compared with males and whether there were statistically significant differences in the percentages of prescriptions for each anti-asthmatic medication among different physician specialties. Analyses were performed using the Statistical Analysis System software, version 6.12 (SAS Institute, Cary, NC, USA).

Results

The study included 226,018 patients, of whom 89,553 (39.62%) were females and 136,465 (60.38%) were males. In every age group, there were fewer female than male patients. For females, the number of patients declined gradually with increasing age from 65 years; for males, there was a peak in the number of patients at 72 years of age. A total of 708,624 prescriptions, including 257,378 (36.32%) for female and 451,246 (63.68%) for male patients, were analyzed. An average of 6.32 different drugs were used in each prescription, of which an average of 1.32 items were anti-asthmatic agents. Of the 4,478,262 prescribed drugs, 936,505 (20.91%) were anti-asthmatics.

Patterns and extent of medication use

Patients were treated most frequently with methylxanthines (49.70%). Only 3.94% and 0.04% of patients received ICSs and cromolyn (inhaled anti-inflammatory agents), respectively. As shown in Table 1,

7.79% of patients were given ISBAs, while 44.03% of patients received OSBAs. Significantly fewer females than males were prescribed each category of anti-asthmatic medication ($p < 0.001$). The only exception was ketotifen, which was prescribed more often for females than for males ($p < 0.001$).

The six most common anti-asthmatic regimens are shown in Table 2. These regimens accounted for 29.89% of all asthma prescriptions. It should be noted that 34.67% of prescriptions did not include any anti-asthmatic agents. The highest percentage of prescriptions (29.19%) contained only one anti-asthmatic item. These included 14.50% with methylxanthine only, 10.90% with OSBAs only, and 1.12% with OCSs only (Table 2). A total of 19.10% of prescriptions contained two anti-asthmatic drugs, and 17.04% of prescriptions contained three or more anti-asthmatic drugs (Figure 1).

Influence of specialty on prescription of anti-asthmatics

General internists accounted for more than half (55.61%) of total prescriptions, followed by general practitioners (20.24%) and family physicians (11.22%). However, prescriptions from pulmonologists, the most desired specialist for treating asthma in the elderly, accounted for only 3.33% of all prescriptions (Figure 2).

Even though pulmonologists contributed the fewest prescriptions, a significantly higher proportion of their prescriptions included inhaled anti-asthmatics compared to those of other practitioners ($p < 0.001$). However, there was no significant difference in the use of cromolyn between pulmonologists and other practitioners. Although 21.29% of prescriptions from pulmonologists contained ISBAs and 19.87% included ICSs, only 7.78% and 4.16% of general internists' prescriptions included ISBAs and ICSs, respectively. Pulmonologists were also more likely to prescribe ipratropium (17.22%) and OCSs (22.37%). However, they were less likely to use ketotifen, which only accounted for 0.59% of their prescriptions (Table 3).

Discussion

There were three main findings from our study: oral anti-asthmatic agents are most often prescribed and

Table 1. Number and percentage of patients prescribed each category of anti-asthmatic medication

Drug	Female (%)	Male (%)	Total (%)	OR	CI	*p* value
ISBA	5,233 (5.84)	12,384 (9.07)	17,617 (7.79)	0.62	0.60–0.64	< 0.001
OSBA	36,525 (40.79)	62,987 (46.16)	99,512 (44.03)	0.80	0.79–0.82	< 0.001
Methylxanthine	41,617 (46.47)	70,720 (51.82)	112,337 (49.70)	0.81	0.79–0.82	< 0.001
Cromolyn	24 (0.03)	84 (0.06)	108 (0.04)	0.44	0.28–0.69	< 0.001
Ketotifen	2,848 (3.18)	3,973 (2.91)	6,821 (3.01)	1.10	1.04–1.15	< 0.001
ICS	2,695 (3.01)	6,211 (4.55)	8,906 (3.94)	0.65	0.62–0.68	< 0.001
Ipratropium	1,903 (2.12)	6,787 (4.97)	8,690 (3.84)	0.42	0.39–0.44	< 0.001
OCS	13,766 (15.37)	21,914 (16.06)	35,680 (15.79)	0.95	0.93–0.97	< 0.001

OR = odds ratio for different asthma treatments for females compared with males; CI = 95% confidence interval; ISBA = inhaled short-acting β-agonist; OSBA = oral short-acting β-agonist; ICS = inhaled corticosteroid; OCS = oral corticosteroid.

Table 2. The six most common anti-asthmatic drug regimens

Regimen	Number of prescriptions	%
Methylxanthines only	102,762	14.50
OSBAs only	77,229	10.90
OSBAs + methylxanthines	13,287	1.88
OCSs only	7,903	1.12
OSBAs + OCSs	5,437	0.77
Methylxanthines + OCSs	5,104	0.72

OSBA = oral short-acting β-agonist; OCS = oral corticosteroid.

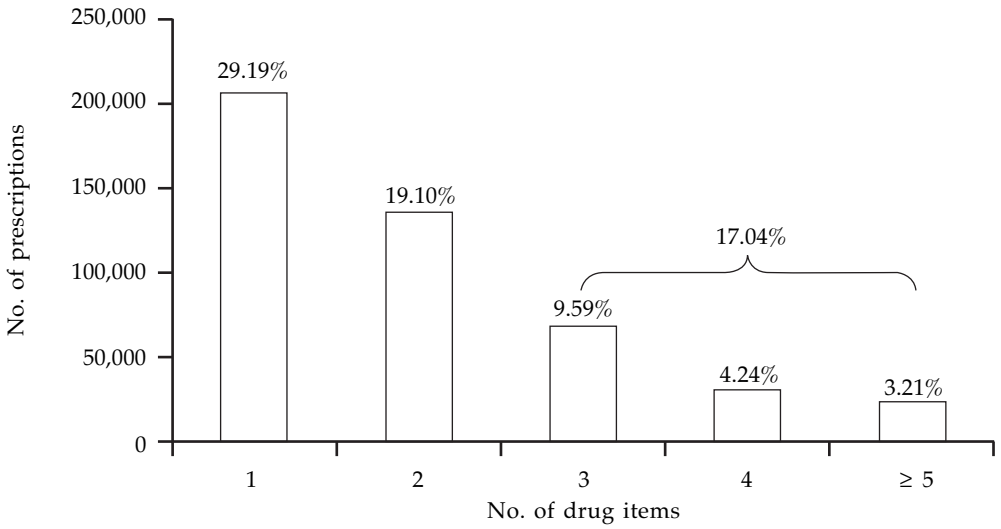

Figure 1. *Number of prescriptions according to the number of anti-asthmatic drug items per prescription.*

ICSs are underused; pulmonologists prescribe significantly more inhaled anti-asthmatics compared to other practitioners ($p < 0.001$); and compared to males, fewer females are prescribed each category of anti-asthmatic medication.

Asthma is primarily regarded as an inflammatory disease and current treatment strategies emphasize anti-inflammatory medications as first-line maintenance or preventive therapy. The daily use of anti-inflammatory medications, such as ICSs, is suggested for all patients with mild to severe persistent asthma [9]. Clinical trials and observational studies have shown that ICS use in adequate amounts prevents asthma symptoms, improves pulmonary physiologic characteristics, and may reduce resource use for asthma attacks [20–24]. There is growing evidence that the persistence of airway inflammation predisposes to airway remodeling, resulting in airway fibrosis and

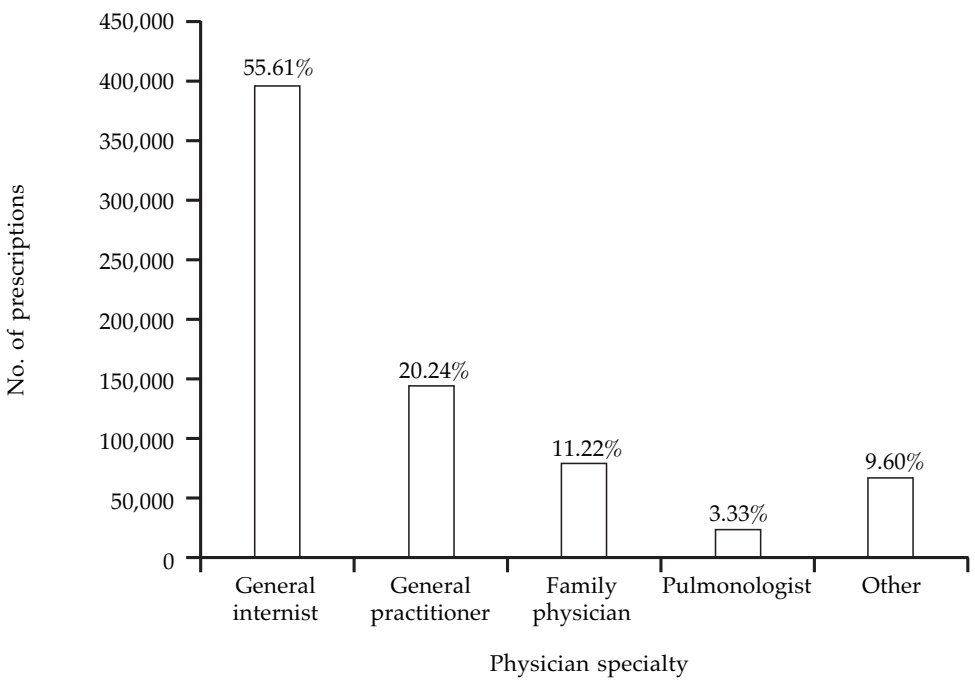

Figure 2. *Number of prescriptions by physician specialty.*

Table 3. Percentage of prescriptions for each anti-asthmatic medication according to physician specialty

Physician specialty	ISBA	OSBA	Methylxanthine	Cromolyn	Ketotifen	ICS	Ipratropium	OCS
General practitioners	2.41	46.94	56.40	0.01	5.21	0.42	2.13	15.60
Family physicians	2.94	42.33	54.89	0.02	3.29	1.08	0.64	11.43
General internists	7.78	42.64	59.06	0.07	1.36	4.16	3.73	12.40
Pulmonologists	21.29*	47.34	63.35	0.05	0.59	19.87*	17.22*	22.37

ISBA = inhaled short-acting β-agonist; OSBA = oral short-acting β-agonist; ICS = inhaled corticosteroid; OCS = oral corticosteroid. *$p < 0.001$ compared to other practitioners.

irreversible airflow obstruction. This risk increases with the increase in the duration of asthma and the age of patients. As a result, adequate treatment with anti-inflammatory agents is particularly pertinent to the elderly asthmatic population [25].

Anti-inflammatory agents continue to be underused by patients and providers around the world [4,5,10]. Our study shows that inhaled anti-inflammatory medications in Taiwan are underused in elderly asthmatic patients to a greater extent than in other countries. Asthma Insights and Reality in Asia Pacific (AIRIAP) has reported that 11%, 14%, and 18% of all asthma patients in Taiwanese samples would be classified as having severe, moderate, and mild persistent asthma, respectively [26]. Therefore, according to current international guidelines, at least 43% of Taiwanese asthmatics should receive daily inhaled anti-inflammatory therapy. However, only 3.94% and 0.04% of elderly asthmatics used ICSs and cromolyn, respectively, in our study. These percentages are far lower than those reported from other countries. In the Cardiovascular Health Study, 30% of geriatric asthma patients were prescribed ICSs [5]. In a community survey, 22% of elderly patients with asthma received ICSs [4]. Hartert et al also report that of patients with moderate or severe asthma, 25% take ICSs [10].

ISBAs should be used on an as-needed basis for quick relief of bronchoconstriction. Due to their quick onset and short duration of action, they are subject to overuse that results in reduced efficacy. Their use has also been associated with increased bronchial hyperreactivity, central nervous system overstimulation, worsening asthma, and death [27,28]. Several recent studies have indicated excessive use of ISBAs. Studies by Pinto Pereira et al [13] and Wolfenden et al [14] found that 95% and 94.6% of patients, respectively, took ISBAs. In our study, 7.79% of patients received ISBA therapy, so overuse of ISBA does not currently appear to be an issue in Taiwan.

The role of ipratropium therapy in asthma is not well defined. Ipratropium has a slower onset of action and is a less potent bronchodilator than ISBAs [29]. Asthma and COPD frequently coexist in the elderly [30]. Patients with COPD may respond to inhaled ipratropium despite a lack of response to β-agonists [31]. In our study, pulmonologists included ipratropium in 17.22% of their prescriptions. Pinto Pereira et al indicate that ipratropium is selectively used in elderly patients (35%), but rarely used in asthmatic patients younger than 65 years [13].

In our study, 15.97% of elderly patients were taking OCSs. This is slightly less than the 18% reported by Enright et al [5]. OCSs have broad anti-inflammatory effects and can substantially reduce the duration and severity of an acute asthma exacerbation. However, they can also cause several adverse side effects in the elderly, including exacerbation of hypertension, abnormalities in glucose metabolism, impaired immune response, osteoporosis, and peptic ulcers. OCSs are reserved for the small proportion of patients with severe persistent asthma [9]. Efforts should be made to minimize the extended use of OCSs in geriatric asthmatics. These include using the lowest possible dose and, perhaps, alternate-day therapy.

OSBAs have slow onset of action and are not suitable for controlling acute asthma. They also cause more side effects than ISBAs, such as tachycardia and hypokalemia. They are not recommended by therapeutic guidelines [9]. Moreover, asthma and cardiovascular diseases frequently coexist in the elderly. Table 1 shows that 44.03% of asthmatic patients in Taiwan are prescribed OSBAs. OSBAs often take the place of ISBAs because they are easy and convenient to administer and, therefore, often used by the elderly.

The use of theophylline, the most common

methylxanthine used in clinical practice, has been reported to increase with age [20]. Hartert et al also showed that theophylline was the most frequently prescribed asthma drug (47%) [10], and as shown in Table 1, methylxanthines are the most frequently prescribed anti-asthmatic agent for the elderly in Taiwan. Methylxanthines have a narrow therapeutic index, more serious side effects than other anti-asthmatics, and great potential for drug–drug interactions. A large proportion of the elderly are usually taking other drugs that may cause excessive serum methylxanthine levels. However, a recent study has shown that theophylline may have anti-inflammatory effects at lower doses than those needed for bronchodilation [32], and this has led to a re-evaluation of its use in patients with asthma. In addition, a once- or twice-daily slow-release oral preparation is available. The use of oral theophylline may improve patient compliance [33], which is particularly important for elderly patients.

Oral anti-asthmatic agents are convenient to administer, but have slower onset of action and more potential for systemic side effects. Therefore, for elderly asthmatics, inhaled medications should be preferred whenever possible. The finding that significant numbers of Taiwanese geriatric asthmatic patients are taking OCSs and/or oral bronchodilators implies that their asthmatic symptoms are poorly controlled. However, in the elderly, neuromuscular-skeletal disorders, weak or deformed hands, and intellectual impairment may disturb inhaler use and discourage the use of inhaled agents in this age group. Inappropriate or insufficient patient education by healthcare providers may also hamper the proper use of medication. Another plausible explanation for the low level of use of inhaled medications in Taiwan may be that patients lack confidence in the effectiveness of inhalers.

Specialists are more likely than generalists to follow contemporary guidelines for asthma management [34]. In our study, pulmonologists prescribed significantly more ISBAs and ICSs compared to other practitioners ($p < 0.001$); 21.29% of their prescriptions contained ISBAs and 19.87% included ICSs. Studies show that patients who receive care from primary-care physicians are less likely to receive ICS therapy compared to patients who receive care from specialists, i.e. under-use of ICSs is more likely in patients of generalists than in patients of pulmonologists [11,12]. Legorreta et al indicate that specialists provide more thorough care than primary physicians when treating patients with asthma, and they also provide more information to their patients about what to do to prevent or control an asthma attack [35]. Wu et al also showed that patients treated by pulmonologists were more likely to receive ICS therapy and have better outcomes during the ensuing year than patients treated by generalists [34]. Our results showed that only 3.33% of all prescriptions were written by pulmonologists. This may, in part, be because there are not enough pulmonologists to meet the needs of the population in Taiwan. There were only 700 pulmonologists in Taiwan at the end of 2002 (3 pulmonologists per 100,000 population) [36]. This greatly restricts the access of patients to these specialists.

The proportions of females treated with ISBAs and ICSs were less than the proportions of males (odds ratio, OR, 0.62, $p < 0.001$; OR, 0.65, $p < 0.001$) (Table 1). This finding is consistent with a study by Roberts and Bateman [37]. There was a similar trend for other anti-asthmatic agents, except ketotifen. Females may be treated less frequently with inhalers because they are more likely to have an improper metered-dose inhaler technique than males [38]. However, studies also show that women, in general, take more prescription drugs than men [39,40]. As a result, even though we have shown that women used significantly less inhaled anti-asthmatics than men in Taiwan, this may not have any clinical significance.

International treatment guidelines indicate that inhaled medications are preferred for elderly patients. However, our results show that only 3.94% and 0.04% of Taiwanese patients take ICSs and cromolyn, respectively. Although excessive use of ISBAs is not an issue among Taiwanese elderly patients with asthma, many of them take OSBAs and oral bronchodilators, which may lead to severe side effects. Physicians in Taiwan should prescribe more inhaled anti-inflammatory agents, such as ICSs, in the treatment of asthma in the elderly, as suggested in international treatment guidelines.

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